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Mini review

P2Y receptors in neuropathic pain

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ABSTRACT

This review summarizes and evaluates the relationship between neuropathic pain and P2Y receptors from inception to 2019. Purinergic receptors have been well studied in recent years using various molecular biological methods. The main research objective of this review is to determine the association of P2Y1, P2Y2, P2Y6, P2Y12 and P2Y13 receptors with neuropathic pain. This review includes the most comprehensive subtypes of P2Y that related to neuropathic pain and the current therapeutic method of neuropathic pain. G protein-coupled P2Y receptors are located on neurons, astrocytes, oligodendrocytes and microglial cells and regulate neurotransmission. Nerve injury is the prime reason for abnormal regulation of P2Y receptor mRNA expression, subsequently, inducing neuropathic pain. Neuropathic pain is a type of chronic pain that is divided into peripheral, central and mixed. Numerous studies demonstrated a positive correlation between the expression level of P2Y receptors and neuropathic pain generation. Also, several reports showed that P2Y short hairpin RNA (shRNA) and P2Y antagonist can be used as an analgesic to relieve neuropathic pain via decreasing P2Y receptor expression level and neural cell activation. However, the transformation process from basic experiments to clinical applications is a long process. Current deficiencies and future research directions are discussed at the end of this review.

1. Introduction

Almost every type of mammalian cell expresses P2-purinoceptors, which are divided into P2X and P2Y receptors (Burnstock and Kennedy, 1985). The main subject of the present review is G protein-coupled P2Y receptors. The first P2Y receptor was cloned in 1993, and there are currently eight accepted mammalian P2Y receptors: P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, P2Y13 and P2Y14 (Abbracchio et al., 2003). Extracellular nucleosides/nucleotides (ATP, ADP, UTP, UDP) activate P2Y receptors, which are identified using molecular docking and other ligand tools (Abbracchio, 2006; Jacobson, 2013). P2Y receptors are pharmacologically subdivided into several groups: (1) P2Y1, P2Y12 and P2Y13 are ADP-preferring P2Y receptors; (2) P2Y11 is an ATP-preferring P2Y receptor; (3) P2Y2 and P2Y4 are UTP-recognizing P2Y receptors; (4) P2Y6 is a UDP-preferring P2Y receptor; and (5) P2Y14 is a UDP-sugar-preferring P2Y receptor (Von Kugelgen and Wetter, 2000). In general, different subtypes of P2Y receptors exhibit different distributions and functions in cells. Different P2Y receptors also couple to distinct functional G proteins: Gq/11 for P2Y1, 2, 4, and 6; Gi for P2Y12 and 13; and Gi/o for P2Y13 and P2Y14(Burnstock, 2007). However, the same subtypes of P2Y receptors couple to different G proteins under different conditions or concentrations of ADP, ATP, UTP or UDP (Abbracchio, 2006). P2Y receptors also couple to ion channels, such as K^+ channels and voltage-gated Ca^{2+} channels, primarily in brain and autonomic neurons.

Neuropathic pain is a type of chronic pathological pain that is characterized by progressive hyperpathia and hyperesthesia. Nervous system disease or damage, such as trauma and injury of the peripheral or central nervous system, spinal cord injuries, viral infection, growth pressure, metabolic dysregulation and ischemia, are the general causes of neuropathic pain (Smith and Sang, 2002). The International Association for the Study of Pain (IASP) classified pain based on five factors in 1994: cause, duration, region, system and intensity of pain (International Association for the Study of Pain, 1994). The most common classifications of neuropathic pain are central neuropathic pain and peripheral neuropathic pain. Nervous system damage, such as spinal cord, brain stem and thalamic damage, primarily cause neuropathic pain.

The roles of extracellular nucleotide signalling in many tissues have been well studied (Yegutkin, 2008) since Burnstock first found that purinergic receptors participated in neural transmission. For example, UDP activates P2Y6 receptors to mediate microglial phagocytosis (Koizumi et al., 2007). These basic regulatory mechanisms of P2Y receptors establish the physiological basis for investigating the

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relationship between P2Y receptors and neuropathic pain. In the generation neuropathic pain, most neural damage produces a reduction in the transmission of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) (Gwak and Hulsebosch, 2011). Microglia are also dramatically activated following nerve injury, which ultimately induces neuropathic pain (Tsuda, 2017). Microglia are environmentally sensitive cells that exhibit a high level of mobility. These cells migrate toward the injured site for phagocytosis (Koizumi et al., 2013). Multiple P2Y receptors in microglia are increased and activated after spared nerve injury (Kobayashi et al., 2012). This pain behaviour continues for a much longer time via P2Y receptor regulation and ATP signalling (Decosterd and Woolf, 2000). P2Y shRNA relieves the symptoms of neuropathic pain via decreasing the expression level of P2Y receptors (Wang et al., 2018).

"P2Y receptor and neuropathic pain" remains a novel research hotspot compared to P2X receptors. Although there have been previous commentary or reviews on purinergic receptors and pain (Inoue and Tsuda, 2012; Burnstock, 2013; Magni and Ceruti, 2013), few reviews have specialized in the relationship between P2Y receptors and neuropathic pain. In recent years, papers on antinociceptive therapeutic methods in relieving P2Y-related neuropathic pain have increased (See Table 1). This review focuses on the role of different P2Y receptor subtypes in neuropathic pain and their potential role in the therapy of neuropathic pain.

2. Role of microglia and satellite cells in P2Y receptors-related neuropathic pain

Neuropathic pain can be divided into peripheral and central neuropathic pain, the most difference between them is the location of nerve injury or disease. Peripheral nerve injury may result in amplification of the signal transmitted to the spinal cord (Sawynok, 2014). Peripheral neuropathic pain (PNP) includes several conditions: trigeminalneuropathic pain, post-herpetic neuralgia (PHN), painful diabetic neuropathy (PDN), human immunodeficiency virus (HIV) neuropathy, and post-traumatic neuralgia (Baron et al., 2010). In dorsal root ganglia, satellite cells (SGCs) surround the cell bodies of primary neurons in sensory ganglia, which provides a condition of bidirectional communication between SGCs and neurons (Magni and Ceruti, 2013). ADP/UDP/UTP is released by injured neurons, whereupon P2Y receptors are activated, leading to SGCs proliferation and neuropathic pain (Fig. 1) (Meacham et al., 2017). SGCs play a role in maintaining of peripheral neuropathic pain. The abnormal expression level of P2Y1, 2, 6, 12, 13 receptors is a marker of peripheral neuropathic pain (Kobayashi et al., 2012). PNP models are created via peripheral nerve transection, ligation, constriction, neuritis, partial ligation or laser injury (Sawynok, 2014). In respect of trigeminal neuropathic pain, bradykinin (BK) plays a role in trigeminal SGCs which can activate neuronal BK receptor and cause the release of calcitonin gene-related peptide (CGRP) (Magni and Ceruti, 2013). CGRP, in turn, stimulated the ERK1/2 MAP kinase signalling pathway in surrounding SGCs and activated SGCs. SGCs finally release multiple pro-inflammatory cytokines and chemokines, which likely further contribute to communication with neurons and also maintain neuropathic pain (Baron et al., 2010).

In terms of central neuropathic pain (CNP), the most common pathogenesis of it is traumatic brain injury, spinal cord injury and myelencephalon vascular injury. Central neuropathic pain ultimately results in the formation of a chronic pain state and central sensitization (Meacham et al., 2017; Hulsebosch et al., 2009). Modelling approaches for CNP include spinal cord ischemia, a clip compression of the thoracic spinal cord, anterolateral lesions of the spinal cord, injection of quisqualic acid, spinal cord contusion and spinal hemisection (Hulsebosch et al., 2009). Central neuropathic pain increases the activation of spinal neurons and induce the abnormal synaptic properties (Meacham et al., 2017). In the condition of central neuropathic pain, microglia and other neurons in the dorsal horn are sustained hyperexcitability after spinal

Table 1
The preclinical studies about P2Y receptors taking part in neuropathic pain in vivo.

P2Y receptor subtypes	Experimental model	Species	Treated with	Antinociceptive effects	Reference
P2Y1	Bone cancer model	Rat	MRS2179 (P2Y1 antagonist)	MRS2179 can inhibit P2Y1R-mediated ERK1/2 signalling in the spinal horn cord and DRG, which changes in rat behavioral pain performance	(Chen et al., 2012)
	Spinal nerve ligation	Rat	MRS2500 (P2Y1 antagonist)	MRS2500 can decrease P2Y1R expression in DRG during the development and maintenance of neuropathic pain in 3 different types of nerve injured models	(Barragán-Iglesias et al., 2016)
P2Y2	Sciatic nerve ligation	Rat	Ulinastatin (serine protease inhibitor)	The early application of ulinastatin can alleviate pain behavior in the rat sciatic nerve ligation model	(Shi et al., 2017)
P2Y6	Chronic constriction injury (CCI) model	Adult male Sprague-Dawley rats	MRS2578 (P2Y6 antagonist)	Intrathecal injection of MRS2578 alleviates pain response in CCI- and UDP-treated rats with a dose-dependent manner	(Huang et al., 2018)
	Spared nerve injury (SNI)	Mice	MRS2578 (P2Y6 antagonist)	A single i.t. or i.p. injection of the low dose MRS2557 did not affect the neuropathic pain. However, the high dose of MRS2557 can even induce behavioral abnormalities including motor impairment	(Syhr et al., 2014)
P2Y12	Diabetic neuropathic pain	Rat	P2Y12 short hairpin RNA (shRNA)	shRNA can decrease the expression of the P2Y12 receptor as well as phosphorylation and activation of P38 MAPK in the DRG of DM rats.	(Wang et al., 2018)
	Spinal nerve ligation	Male Wistar rats	AR-C69931MX (P2Y12 antagonist)	AR-C69931MX can decrease mRNA and protein levels in the ipsilateral spinal cord after nerve injury and that this expression is highly restricted to microglia	(Tozaki-Saitoh et al., 2008)
	HIV gp120-induced neuropathic pain	Rat	P2Y12 short hairpin RNA (shRNA)	P2Y12 shRNA treatment decreased HIV gp120-induced mechanical and thermal hyperalgesia in gp120-treated rats	(Shi et al., 2018)
P2Y13	STZ-induced diabetic neuropathic pain	Rat	MRS2211 (P2Y13 antagonist)	MRS2211 can reduce the expression of the P2Y13 receptor, Iba-1, IL-1β, and IL-6 4 weeks after the STZ injection.	(Zhou et al., 2018)
	Chronic constriction injury	Adult male Sprague-Dawley rats	AM1241 (CB2 receptor agonist)	The activation of CB2 receptor can induce the decreased expression of P2Y13, which relieves neuropathic pain	(Niu et al., 2017)

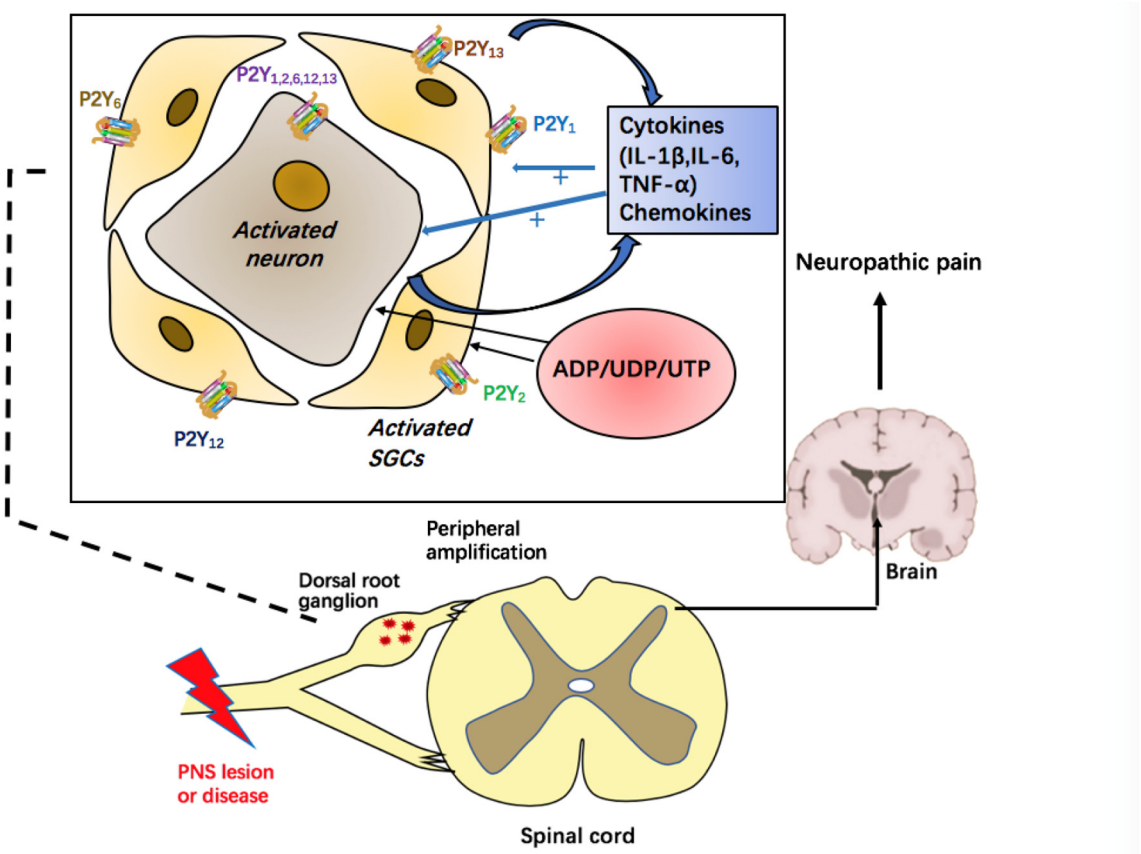

Fig. 1. Peripheral neuropathic pain is caused by PNS lesion or other disease. In dorsal root ganglion, there is a communication between surrounding satellite ganglia cells (SGCs) and neurons. Under the condition of nerve injury, P2Y receptors are activated and expressed at high level in SGCs and neurons via diffusible ADP/UDP/UTP. Activated SGCs and neurons release cytokines and chemokines to stimulate each other and modulate neuropathic pain (see text for details), which causes the peripheral amplification. The peripheral amplification enters to spinal cord and then the nerve impulse transmits to brain and generates neuropathic pain.

cord injury (Hulsebosch et al., 2009). Central nerve lesions activate microglia within the central nervous system (CNS) to release some immune modulators that maintain neuropathic pain, which exhibits similar mechanisms as peripheral neuropathic pain (Baron et al., 2010). Thus, the modulation and maintaining of central neuropathic pain is based on the communication between neurons and microglia (Inoue and Tsuda, 2012) ADP/UDP/UTP is released by injured dorsal horn neurons, whereupon microglial P2Y receptors are activated, leading to microglial proliferation and neuropathic pain (Fig. 2) (Meacham et al., 2017). The mechanisms of CNP are also associated with increased activation of intracellular signalling kinases and transcription factors (Hulsebosch et al., 2009). Several protein kinases participate in central neuropathic pain including PKA, PKC, p38 MAPK, Src, ERK, NMDA-NR2B, and CaMKII (Castany et al., 2018). Spinal pro-inflammatory cytokines, including tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6 also play important roles in the maintenance of neuropathic pain (Fig. 2) (Castany et al., 2018). Activated microglia are known to secrete a number of diffusible pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α, which was hypothesized to contribute to nerve injury-induced neuropathic pain (Inoue and Tsuda, 2006). The detailed presentation of pro-inflammatory cytokines is showed respectively in the Subsection 3. There was a study indicated that microglia activation and pro-inflammatory cytokines production may be most important in the initiation of hypersensitivity and helping to transition to chronic neuropathic pain (Peng et al., 2016). Microglia also express and release neurotrophic factors such as brain-derived neurotrophic factor (BDNF), a neurotransmitter implicated in nociceptive hypersensitivity that follows sensitization and inflammation (Thompson et al., 2002). The most representative CNP is post-stroke pain (Siniscalchi et al., 2012). One report used a labelled P2Y12 receptor to display its localization and expression level in microglia and specifically applied the label in areas of secondary neurodegeneration post-stroke pain (Kluge et al., 2017).

3. Subtypes of P2Y receptors related to neuropathic pain

3.1. P2Y1

The first P2Y1 receptor was cloned from chick brain, and it was subsequently cloned in turkey, rat, mouse, human, and Xenopus (O'Grady et al., 1996; Ayyanathan et al., 1996). P2Y1 receptors modulate neurons, astrocytes and microglia to control neurotoxicity and cognitive deficits (Carmo et al., 2014). P2Y1 receptors are broadly expressed throughout the human body, which suggests that it regulates many physiological processes, such as mediating ADP-induced platelet shape changes and calcium mobilization (Jin et al., 1998). In particular, ADP induced an increase of intracellular Ca^{2+} in transfected human astrocytoma cells and activation of p38MAPK (Gustafsson et al., 2011). The radioligand [125I] MRS2500 investigated the expression levels of P2Y1 receptors on human and mouse platelets in 2010, and the densities of binding sites were different between human and mouse platelets (Ohlmann et al., 2010). Prior to that research, Waldo et al. demonstrated that [3H] MRS2279 specifically bound to human P2Y1, and nucleotide agonists exhibited different affinities: 2-MeSADP > ADP > 2-MeSATP > ATP (Waldo and Harden, 2004). The novel antagonist BPTU was found to block P2Y1 receptors at the neuromuscular junction of the gastrointestinal tract in 2016 (Mañé et al., 2016).

Unfortunately, there are few reports about the relationship between P2Y1 receptors and neuropathic pain. A 2012 study showed that the

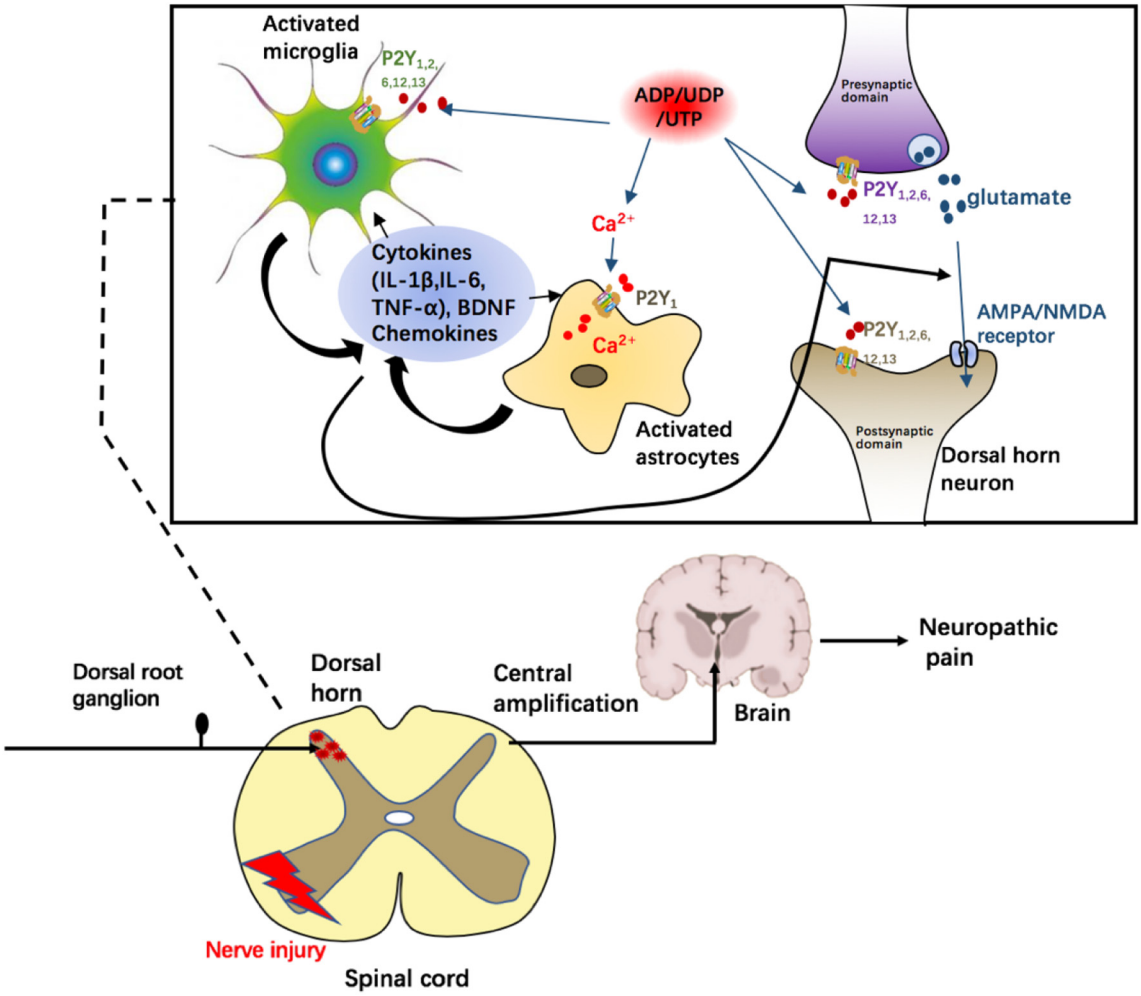

Fig. 2. Central neuropathic pain is caused by CNS lesion or other disease. The related nerve injury causes the neurons, microglia and astrocytes in dorsal horn sustained hyperexcitability. The expression level of P2Y receptors are increased in the cells of dorsal horn via diffusible ADP/UDP/UTP. There is a cross-communication between neurons, microglia and astrocytes via releasing cytokines and chemokines (see text for details). ADP induces an increase of intracellular Ca^{2+} in astrocytes and then activates astrocytes. Besides, the diffused cytokines, chemokines and BDNF induce the release of glutamate from presynaptic domain and also increase the binding rate of glutamate and AMPA/NMDA receptors on postsynaptic domain. Then, the nerve impulse transmits through ascending axon of anterolateral tract and produces the central amplification. Finally, the maladaptive, low-threshold pain causes the disorder.

P2Y1R antagonist MRS2179 attenuated nociceptive transmission (Chen et al., 2012). MRS2179 is a specific inhibitor of P2Y1R, and it reversed tactile allodynia and spontaneous pain in CIBP (cancer-induced bone pain) rats. This study injected the P2Y1R antagonist MRS2179 intrathecally, which decreased P2Y1R mRNA and p-ERK1/2 protein expression in the spinal dorsal horn and dorsal root ganglia (DRG). This study hypothesized that MRS2179 attenuated the expression of P2Y1R mRNA. Of course, other P2Y receptors may also attenuate neuropathic pain.

Barragán-Iglesias et al. (2016) found that P2Y1 receptors were expressed in ipsilateral DRG and the dorsal part of the spinal cord in rat models of neuropathic pain (Barragán-Iglesias et al., 2016). Specifically, chronic constriction injury (CCI), spared nerve injury (SNI) and spinal nerve ligation (SNL) increased the expression of P2Y1 receptors in the DRG, but not in the spinal cord, 1–3 days after injury. Intrathecal injection of the antagonist MRS2500 reduced P2Y1 receptor expression in DRG under these conditions and produced an antiallodynic effect. Notably, Barragán-Iglesias found that MRS2500 increased the 50% withdrawal threshold, which is considered an antiallodynic effect. He also observed that different administration routes (intrathecal versus intraperitoneal) of P2Y receptor antagonists produced opposite effects.

3.2. P2Y2

P2Y2 receptors are widely expressed in many organs, such as liver, lung, epithelial tissues, spleen, kidney, and breast (Abbracchio, 2006; Tak et al., 2016; Boucher et al., 2010). P2Y2 receptors bind UTP and ATP. Activated P2Y2 receptors regulate the nociceptor phenotype (Tak et al., 2016). Extracellular ATP or UTP is involved in the activation of sensory neurons, the transmission of sensory signalling and phosphorylation of CREB (cAMP-response element binding protein) in neurons (Molliver et al., 2002). P2Y2 mRNA is widely expressed in the DRG and trigeminal neurons (Molliver et al., 2002).

P2Y2 receptors in satellite glial cell may be a “druggable” target in the treatment of trigeminal neuropathic pain (Magni et al., 2015). Many reports showed that ATP and P2X receptors regulated trigeminal neuropathic pain. G protein-coupled P2Y2 receptors are related to trigeminal neuropathic pain (Li et al., 2014). UTP as an agonist of P2Y2 receptors, and it induces hyperalgesia in rats. Inhibition of P2Y2 receptor activation downregulated ERK-mediated phosphorylation and upregulated the expression of fast-inactivating transient K^+ channels (I_A)–related Kv channels in trigeminal ganglion neurons (Li et al., 2014). Therefore, P2Y2 receptors play a role in maintaining allodynia in trigeminal neuropathic pain.

A 2017 report indicated that the serine protease inhibitor

ulinastatin relieved neuropathic pain via regulation of the ATP/P2Y2 receptor pathway in rat (Shi et al., 2017). The chronic constrictive nerve injury increased the expression level of P2Y2 receptors in rat microglia and abnormally activated microglia in the dorsal horn of the spinal cord (Shi et al., 2017). In this study, ulinastatin reduced AMPK expression in the spinal cord and inhibited the ATP/P2Y2 receptor pathway. However, ulinastatin is best used for the early stage of neuropathic pain, which is primarily confined to symptom control, or as a prophylactic (Shi et al., 2017).

3.3. P2Y6

Chang et al. cloned the UDP-sensitive P2Y6 receptor from rat aortic smooth muscle in 1995 (Chang et al., 1995). In 1996, the human P2Y6 receptor mRNA was detected in human spleen, placenta and other organs by Communi et al. (Communi et al., 1996). P2Y6 receptors are expressed in many tissues and organs (human spleen, placenta, thymus and blood leukocytes), which were well studied. P2Y6 receptors also participate in many regulating pathways in the human body, especially the immune system and nerve system (Communi et al., 1996). For example, P2Y6 receptor expression was developmentally increased in vascular smooth muscle cells, which may treat cardiovascular diseases (Nishimura et al., 2017). The P2Y6 receptor is related to activation of phospholipase C (PLC) inositol lipid signalling and intracellular calcium, and it is coupled to the Gq/11 protein (Syhr et al., 2014).

The contribution of P2Y6 receptors to neuropathic pain processing is less well studied compared to other P2Y receptors. Syhr found that P2Y6 receptor were expressed in the central terminals of primary afferent neurons of the mouse spinal cord, and their expression was upregulated following peripheral nerve injury. Syhr et al. injected the P2Y6 receptor antagonist MRS2557 to compare the function of the P2Y6 receptor and the other subtypes of P2Y receptors (Syhr et al., 2014). They found that the P2Y6 receptor played only a limited role in the processing of peripheral nerve injury-induced neuropathic pain in mice (Syhr et al., 2014). Specifically, a single i.t. or i.p. injection of a low dose MRS2578 did not affect the neuropathic pain. A high dose of MRS2578 induced behavioral abnormalities, including motor impairment. Huang (2018) demonstrated a dose-dependent effect of MRS2578 in relieving neuropathic pain. He used mechanical withdraw threshold and paw thermal withdraw latency to analyse the changes in rat behaviour (Huang et al., 2018). Specifically, MRS2578 at 10^{-9} M produced slight but significant thermal and mechanical anti-hyperalgesic effects (Huang et al., 2018). MRS2578 at 10^{-6} M to 10^{-4} M produced significant anti-hyperalgesic effects, and these effects lasted for 7 days (Huang et al., 2018). Treatment with MRS2578 decreased the expression of P2Y6 receptors and Iba-1 mRNA (Huang et al., 2018).

P2Y6 receptors are also expressed on microglial cells and some brain immune cells. When neurons were damaged, P2Y6 receptors were activated and upregulated via diffusible UDP in microglia (Koizumi et al., 2007). These microglial cells induced phagocytosis. Several studies showed that antagonists of P2Y6 receptors reduced tactile allodynia in spinal nerve-ligated rats (Syhr et al., 2014; Barragán-Iglesias et al., 2014). There was an inhibitory crosstalk between metabotropic UDP P2Y6 and ATP-gated P2X4 receptors based on a PIP2 hydrolysis-dependent mechanism in microglia (Bernier et al., 2013). However, whether these 2 receptors also exhibit an antagonistic relationship in the regulation of neuropathic pain is no known.

3.4. P2Y12

The human P2Y12 receptor was cloned in 2001, and it was a better anti-platelet agent, which suggests that P2Y12 receptors participate in the treatment of cardiovascular diseases (Hollopeter et al., 2001). P2Y12 receptors play a crucial role in platelet activation and induce thrombogenesis (Cattaneo and Podda, 2010). P2Y12 receptors couple to Gi and respond to ADP. Two potential N-linked glycosylation sites modulate its activity (Zhong et al., 2004). Four specific antagonists of P2Y12 receptors were tested in clinical trials: clopidogrel, prasugrel, cangrelor and ticagrelor (Cattaneo and Podda, 2010).

Several studies showed that microglia cells were critical in the pathogenesis process of neuropathic pain (Gu et al., 2016; Von Kügelgen and Hoffmann, 2016). Microglia are surveillance cells that perform homeostatic functions to maintain the health of the CNS. The expression of P2Y12 receptors was increased in microglia at the mRNA and protein levels in the ipsilateral spinal cord in animal models of nerve injury. The p38 MAPK pathway was activated, and neuropathic pain was generated under this condition (Kobayashi et al., 2008; Tozaki-Saitoh et al., 2008). After nerve injury, microglia produce proinflammatory cytokines and other effectors to stimulate nociception in the spinal cord (Kobayashi et al., 2008). There was a study used intrathecal administration of the antagonist AR-C69931MX to block microglial P2Y12 receptors and inhibit tactile allodynia after nerve injury (Tozaki-Saitoh et al., 2008). However, the mechanism of the P2Y12-dependent increase in microglial surveillance during neuropathic pain is not clear.

The P2Y12 gene regulates many other types of neuropathic pain. One of the most recent reports indicated that P2Y12 shRNA may be used to relieve HIV glycoprotein 120 (gp120)-induced and gp120 + ddC (2′,3′-dideoxycytidine)-induced neuropathic pain in rats. This result was a novel discovery for the treatment of HIV-related neuropathic pain (Wang et al., 2018; Shi et al., 2018; Yi et al., 2018). The studies also showed that P2Y12 receptor activated satellite glial cells (SGCs) in the DRG (Shi et al., 2018; Yi et al., 2018).

Diabetic neuropathic pain is one complication of diabetes, and it also involves P2Y12 regulation (Jia et al., 2018). Diabetic patients suffer hyperalgesia and allodynia as a result of their neuropathic pain (Archer et al., 1983). Studies showed increased levels of P2Y12 receptor expression in diabetic rat models. The upregulated P2Y12 receptors also activate SGCs in the process of diabetic neuropathic pain (Jia et al., 2018).P2Y12 short hairpin RNA (shRNA) decreased satellite glial cells activation and relieved diabetic neuropathic pain (Wang et al., 2018). Another study showed that nanoparticle-encapsulated curcumin inhibited diabetic neuropathic pain (Jia et al., 2018). Curcumin may bind to the P2Y12 protein to limit the interaction between the P2Y12 receptor and its agonist, leading to the inhibition of the P2Y12 receptor in the SGCs of DRG and reduced mechanical and thermal hyperalgesia in DM rats. In addition, curcumin inhibited the activation of SGCs and decreased the up-regulated IL-1β and Cx43 expression levels, reduced levels of phosphorylated-Akt (p-Akt) in the DRG of rats with DM.

3.5. P2Y13

The P2Y13 receptor is a novel human ADP receptor that is closely related to the human P2Y12 receptor, which was found and cloned in 2001 (Communi et al., 2001). The P2Y13 receptor was detected using RT-PCR, and it had high expression in spleen and brain (Communi et al., 2001). P2Y12 and P2Y13 receptors couple to Gi and have a high affinity for ADP, despite exhibiting different structures (Communi et al., 2001). The P2Y13 receptor exhibits a neuroprotective action that against glutamate excitotoxicity (Ortega et al., 2011). P2Y13 and P2X7 receptors activate the ERK signalling pathway and maintain the normal condition of cerebellar granule neurons (Ortega et al., 2011).

One study indicated that P2Y12 and P2Y13 receptors exhibit synergistic effects in the regulation of neuropathic pain (Tatsumi et al., 2015). The expression level of P2Y13 receptors increases after nerve injury (Tatsumi et al., 2015). The RhoA/ROCK pathway was activated in microglia, which caused neuronal excitability and neuropathic pain (Tatsumi et al., 2015). This pathway mediates p38 MAPK activation, which sparked treatment for P2Y13-related neuropathic pain (Communi et al., 2001). In 2017, scientists found that CB2 receptors in dorsal spinal cord microglia suppressed P2Y13 receptor expression (Niu et al., 2017). AM1241 is a CB2 receptor agonist, and it inhibited P2Y13

receptor expression via p38MAPK/NF-kappa B signalling (Niu et al., 2017). In addition, P2Y13 receptors in the dorsal horn are also related to diabetic neuropathic pain (DNP) (Zhou et al., 2018). In the early stage of diabetic neuropathic pain rat models, P2Y13 receptors promote the expression of the proinflammatory cytokines interleukin (IL)-1β and IL-6 at the spinal dorsal horn (Zhou et al., 2018). MRS2211 can decrease the P2Y13 receptor activation and downregulates the levels of IL-1 and IL-6, which subsequently inhibit activation of the JAK2/STAT3 signalling pathway. This study demonstrated that MRS2211 produced an anti-nociceptive effect in early-stage DNP.

4. Conclusion and future directions

The most common cause of neuropathic pain is nerve injury. One of the necessary indicators of neuropathic pain is the expression level of P2Y receptors in nerve cells, including P2Y1, P2Y2, P2Y6, P2Y12 and P2Y13, which was recorded by many researchers and summarized in this review. All of these receptors exhibit similar functions in the process of neuropathic pain, but their mechanisms are different. Our review summarized the different structures and pharmacology of P2Y receptors separately, and the different mechanisms of these receptors in mediating neuropathic pain were also summarized in detail. Some receptors also inhibit the function of other types of P2Y receptors. For example, P2X4 inhibits the function of P2Y6 receptors in microglia, and CB2 receptors inhibit the function of P2Y13 receptor in process of neuropathic pain.

In terms of the prevention and treatment of neuropathic pain, recent studies of P2Y receptors provide some novel ideas. P2Y receptor subtypes increase after nerve injury but before the onset of neuropathic pain, and the expression level of P2Y receptors subtypes is an indicator of neuropathic pain. Therefore, it is possible to prevent the development of neuropathic pain at its initiation. On the other hand, early application of P2Y receptor antagonists may help control the development of neuropathic pain. We also mentioned some early-stage treatments of neuropathic pain related to P2Y receptors, such as ulinastatin (decrease P2Y2 receptors expression) and MRS2211 (P2Y13 antagonist). Therefore, among the P2Y receptor-related drugs, the types of drugs used for prevention and early treatment are definitely different. With further improvements of P2Y receptor-related drug research, patients with neuropathic pain may be able to choose different drugs in different courses of the disease in the future.

In general, antidepressants and anticonvulsants are traditional first-line drugs for the treatment of neuropathic pain. However, P2Y receptor shRNA and antagonists are not used in clinical treatment. No studies have examined the side effects of the P2Y receptor-related RNA interference therapy or P2Y receptor antagonists. Therefore, the next necessary research direction is exploring the feasibility of gene interference therapy and P2Y receptor antagonists to treat neuropathic pain. Many problems must be resolved and discussed in future studies. For example, the signal transduction pathway of P2Y receptors is not very clear, which causes difficulty in developing therapeutic methods to treat new types of neuropathic pain. Development of a useful complication prevention method for many related diseases is also necessary.

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